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HEALTH EFFECTS ASSESSMENT FOR ACETONE

U.S. Environmental Protection Agency
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A subchronic and chronic interim acceptable intake was determined for acetone based on inhalation exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with acetone. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1981. Criteria Document for Acetone. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal Draft.

U.S. EPA. 1983b. Disposition of Comments on Criteria Document for Acetone. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal Draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The AIC for acetone, 209.6 mg/day, is based on a subchronic (8-week) animal exposure study showing reversible changes following exposure to 19,000 ppm acetone. Although data are extremely limited, fragmentary human data at similar exposure concentrations indicate no adverse effects. In addition, this AIC is below that which could be calculated from the most conservative occupational exposure guidelines (NIOSH, 1978). This estimate may be conservative and reflects the limited data base. Data were inadequate to estimate an AIS or AIC for oral exposure and were also insufficient for derivation of a CS.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
LD_{50}	Dose lethal to 50% of recipients
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of acetone (CAS No. 67-64-1) are as follows:

Molecular weight:	58.08	
Chemical class:	aliphatic ketone	
Vapor pressure:	185.95 mm Hg at 20°C	U.S. EPA, 1981
Water solubility:	miscible with water	U.S. EPA, 1981
Log octanol/water partition coefficient:	-0.24	U.S. EPA, 1981
BCF:	0.69 in haddock muscle (Melanogrammus aeglefinus) 0.12 (estimated)	U.S. EPA, 1981
Half-lives in Air:	14 hours	Graedel, 1978
Water:	10 hours to 9 days	U.S. EPA, 1981

The BCF value of 0.12 has been estimated from the equation of Veith et al. (1979) and the log octanol/water partition coefficient given above.

The value for the half-life of acetone in the atmosphere is based on its photochemical reaction and the rate constant for the photochemical reaction given by Graedel (1978). The half-life of acetone in water is based on its evaporation rate from quiescent to different aerated conditions. The biodegradation half-life may be comparable to its evaporation half-life under certain conditions; however, biodegradation has not been considered in estimating the aquatic half-life of acetone because of the lack of available rate constant data.

The half-life of acetone in soil could not be located in the literature searched; however, evaporation is expected to be the predominant loss mechanism from the soil surface. By analogy with the biodegradation studies of acetone in other media (U.S. EPA, 1981), it is likely that it will undergo significant biodegradation in soils as well. The undecomposed acetone is expected to leach from soil because of its high water solubility and expected weak sorption on soils. The detection of acetone in both soil leachate and groundwater is evidence for its soil leachability (U.S. EPA, 1981).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although absorption factors were not reported, several studies indicate that acetone is readily absorbed through the gastrointestinal tract in humans and animals.

Schwartz (1898) administered acetone either orally or subcutaneously to dogs. For both routes of exposure, 59-76% of the administered dose was eliminated through expired air, while 1.5-4.7% was excreted in the urine.

Haggard et al. (1944), Parmeggiani and Sassi (1954), and Price and Rittenberg (1950) also reported that orally administered acetone was eliminated through expired air and in the urine.

2.2. INHALATION

Numerous reports indicate that acetone is absorbed through the pulmonary route of exposure. Dalhamn et al. (1968) demonstrated that 60% of the inhaled dose of acetone (~1 mg in cigarette smoke) was absorbed by humans within 2 seconds of contact. Haggard et al. (1944) reported that the absorption of acetone through inhalation in rats is rapid and dose-related, reaching steady-state after 2 days of continuous exposure. Similar results were obtained with volunteers; however, steady-state was not achieved because these individuals were exposed for only 8 hours. Furthermore, greater absorption of acetone was observed in the volunteers who exercised during inhalation.

In an experiment similar to that of Haggard et al. (1944), DiVincenzo et al. (1973) determined that light exercise (a cycle of jogging for 5 minutes followed by 10 minutes of rest) approximately doubled the postexposure levels of acetone in the expired breath of volunteers. Wigaeus et al.

(1981) also reported that the absorption of acetone through inhalation in volunteers increased with exercise, but added further that the relative uptake (39-52%) was not affected by the workload.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Very little information regarding the subchronic toxicity of orally administered acetone was located in the available literature. Sollman (1921) exposed three rats to 2.5% acetone in drinking water for 18 weeks. Upon termination of the experiment, the animals were found to be "practically normal," experiencing only weight loss, which might have been due to decreased food consumption. No other endpoints were examined or reported.

3.1.2. Inhalation. Information regarding the subchronic toxicity of inhaled acetone is also limited. Bruckner and Peterson (1981) exposed rats to vapors of acetone at levels of either 0 or 19,000 ppm for 3 hours/day, 5 days/week for 8 weeks. Groups of four rats were killed and examined at 2, 4 and 8 weeks throughout exposure and at 2 weeks postexposure. Narcosis was seen in animals exposed to acetone. These animals, however, had no changes in clinical chemistry variables or histological changes in the liver, brain, kidneys, lungs or heart regardless of when they were examined. Slight decreases in organ weights and body weights were observed in rats killed during exposure but not in rats killed 2 weeks postexposure.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic toxicity of orally administered acetone were not located in the available literature.

3.2.2. Inhalation. In two other occupational exposure studies, workers exposed to vapors of acetone at either 19-920 ppm (Parmeggiani and Sassi, 1954) or >750 ppm (Raleigh and McGee, 1972) complained of irritation of the mucosal membranes, including conjunctivitis, pharyngitis, inflammatory bronchitis and gastroduodenitis.

Oglesby et al. (1949) examined the physical condition, and hematological and urological variables in 800 men exposed occupationally to vapors of acetone (600-2150 ppm). These men were examined once a year from 1931 to 1948. There were no statistically significant differences between these men and a group of 800 controls with respect to any of the variables measured, though transient eye and nose irritation was experienced by some of the exposed workers. This study indicates that exposure to <2150 ppm acetone for <8 hours/day produces no significant toxic effects.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of ingested acetone were not located in the available literature; however, acetone is known to cross the placenta (Dowty et al., 1975).

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled acetone were not located in the available literature.

3.4. TOXICANT INTERACTIONS

A number of studies indicate that acetone potentiates the hepatotoxic effects of carbon tetrachloride (Traiger and Plaa, 1973; Plaa et al., 1975, 1982; Folland et al., 1976), 1,1,2-trichloroethane and 1,1,1-trichloroethane (Traiger and Plaa, 1973; Plaa et al., 1975; MacDonald et al., 1982), and Br_2CHCl and trichloroethane (Hewitt et al., 1983). Acetone was also reported to antagonize semicarbazide-induced convulsions in rats (Kohli et al., 1967), but had an additive effect upon LD_{50} in rats treated with acetonitrile (Smyth et al., 1962).

Glatt et al. (1981) reported that acetone enhanced the mutagenic activity of dimethylnitrosamine in *in vitro* assays but not *in vivo* assays.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of ingested acetone were not located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled acetone were not located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenicity of orally administered acetone were not located in the available literature.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled acetone were not located in the available literature.

4.3. OTHER RELEVANT DATA

Acetone did not show mutagenic activity when tested in microbial assay systems (McCann et al., 1975; Abbondandolo et al., 1980; Maron et al., 1981; Haellstrom et al., 1981) or in cell transformation systems (Freeman et al., 1973; Rhim et al., 1974; Quarles et al., 1979a,b). Furthermore, acetone gave negative results in assays that tested for chromosomal aberrations and sister chromatid exchange (Norppa et al., 1981; Norppa, 1981; Tates and Kriek, 1981), DNA cell binding (Kubinski et al., 1981), point mutation in mouse lymphoma cells (Amacher et al., 1980) and transfection (Vasavada and Padayatty, 1981). In one study, however, acetone was reported to produce chomosomal aberrations but not sister chromatid exchange (Kawachi et al., 1980).

4.4. WEIGHT OF EVIDENCE

Pertinent data regarding the carcinogenicity of acetone in humans or in experimental animals were not located in the available literature. The evidence for the carcinogenicity of acetone in humans is appropriately

designated as inadequate. Using the scheme for the classification of the carcinogenicity of chemicals to humans proposed by the Carcinogenic Assessment Group of the U.S. EPA (Federal Register, 1984), acetone is most appropriately designated a Class D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1983) has recommended a TLV-TWA of 750 ppm and a STEL of 1000 ppm for occupational exposure to acetone. These values were chosen to prevent nose and eye irritation (ACGIH, 1980). NIOSH (1978) has recommended a criterion of 250 ppm for exposure to acetone in the workplace, while OSHA has adopted 1000 ppm as a standard for occupational exposure to acetone (Code of Federal Regulations, 1981).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. The only subchronic oral study located in the available literature was that of Sollman (1921). Data from this study cannot be used to derive an AIS or a CS because small numbers of animals were used; there was only one level of exposure; and histological endpoints were not examined and control animals were not maintained.

6.1.2. Inhalation. Bruckner and Peterson (1981) reported that rats experienced narcosis during the 3-hour exposure periods to 19,000 ppm acetone. In addition, body weight was slightly decreased in rats during the 8 weeks of treatment; however, body weight returned to control values by 2 weeks after cessation of exposure (Bruckner and Peterson, 1981). A NOAEL of 19,000 ppm can be established on the basis of reversible changes in organ and body weights in rats.

Using the NOAEL of 19,000 ppm (45,134 mg/m^3), the animal dose in mg/kg/day can be calculated by assuming a rat breathes 0.26 m^3/day and weighs 0.35 kg, and by expanding the exposure from a 3-hour, 5 days/week intermittent exposure to a continuous exposure as follows:

$$\text{mg/kg/day} = 45{,}134\ \text{mg/m}^3 \times 0.26\ \text{m}^3/\text{day} \times 3/24 \times 5/7 \div 0.35\ \text{kg} = 2994\ \text{mg/kg/day}$$

To calculate the AIS, this animal dose is multiplied by the assumed average human body weight of 70 kg and divided by an uncertainty factor of 100 (a factor 10 for converting an animal NOAEL to a human NOAEL and another factor of 10 to protect the more sensitive individuals of a population). The AIS thus derived for acetone is 2096 mg/day.

Although exposure duration was only 3 hours/day, the extrapolation to a 24-hour day, 7 days/week exposure actually reduced the exposure concentration by more than a factor of 10 before uncertainty factors were applied. The extrapolation is acceptable because this compound does not accumulate in tissues, including fat, and it is rapidly excreted in expired air and in urine. Furthermore, there appear to be no major systemic effects other than narcosis even at unusually high exposure levels. The estimate of an AIS for inhalation in mg/kg implicitly assumes that the exposure will be spread uniformly over a day.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Data are insufficient to calculate an AIC for chronic oral ingestion of acetone. Data from which a CS for oral exposure to acetone can be calculated have not been located in the available literature.

6.2.2. Inhalation. The study by Oglesby et al. (1949) suggested a NOAEL at <21,500 ppm for workers exposed to acetone, but the lack of properly matched controls and uncertainties about levels of exposure preclude the use of this study in quantitative risk assessment.

An interim chronic inhalation ADI can be derived from the interim subchronic inhalation ADI of 2096 mg/day by applying an additional uncertainty factor of 10 to convert subchronic to chronic exposure. This results in an AIC of 209.6 mg/day for a 70 kg human. This estimate is in the same range, but more conservative than an estimate that could be derived using the most conservative criterion for occupational exposure [NIOSH, 1978 (250 ppm)]. The estimate of an AIC for inhalation in units of mg/day implicitly assumes that the exposure will be uniformly spread over the day. Data from which a CS for inhalation exposure to acetone can be calculated have not been located in the available literature.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Data are insufficient to calculate a q_1^* for oral exposure to acetone.

6.3.2. Inhalation. Data are insufficient to calculate a q_1^* for exposure to acetone by inhalation.

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APPENDIX

Summary Table for Acetone

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	rat	19,000 ppm	transient decrease in body weight	2096 mg/day	Bruckner and Peterson, 1981
AIC	rat	19,000 ppm	transient decrease in body weight	209.6 mg/day	Bruckner and Peterson, 1981
Maximum composite score				ND	
Oral					
AIS	NA	NA	NA	ND	NA
AIC	NA	NA	NA	ND	NA
Maximum composite score				ND	

ND = Not derived; NA = not applicable